COMPARATIVE STUDY OF VARIOUS TREATMENT MODALITIES FOR PATIENTS WITH KELOID

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CERTIFICATE

Certified that this dissertation entitled ***"COMPARATIVE STUDY OF VARIOUS TREATMENT MODALITIES FOR PATIENTS WITH KELOID"*** is a bonafide work done by **DR. S.MADHAVI,** Post Graduate Student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 600 003, during the academic year 2008 – 2011. This work has not previously formed the basis for the award of any degree.

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CONTENTS

INTRODUCTION:

Collagen synthesis and collagen degradation take place in a strictly controlled state of equilibrium. Loss of this equilibrium, results in abnormal tissue repair. Excessive collagen synthesis and / or degradation may lead to one of the most challenging sequels in the clinical practice.

Keloid scars are one of the most challenging problems for physicians and surgeons. These scars have been treated in many ways with varying success. In our study, we are comparing 5 different treatment modalities in the management of keloid.

REVIEW OF LITERATURE:

DEFINITION OF A SCAR:

A scar can be defined as a macroscopic disturbance of the normal structure and function of the skin resulting from the end product of a healed wound.

NORMAL PROCESS OF WOUND HEALING:

Wound healing is a natural restorative response to tissue injury. It has 3 classic phases. A) Inflammation B) Proliferation C) Maturation.

Proliferation includes a) Epithelisation b) Fibroplasia c) Angiogenesis

INFLAMMATION: Wounding of skin disrupts tissue and blood vessels leading to a direct exposure of extracellular matrix to platelets. Platelets release cytokines like PDGF, TGF –β, serotonin and fibronectin. A fibrin clot is formed which acts as a scaffold for neutrophils, monocytes, macrophages and lymphocytes which release a number of cytokines.

PROLIFERATION: There is a proliferation of fibroblasts and endothelial cells due to the action of VEGF and TGF-β. Early granulation tissue is formed which is characterised by myofibroblasts that contain elevated levels of α smooth muscle actin. Then there is proliferation and migration of epithelial cells adjacent to the wound.

MATURATION: This is characterised by reorganization of collagen. Early matrix is composed of fibronectin and collagen type 3 which is replaced by final matrix which is composed of glycosaminoglycans, proteoglycans and collagen type 1[1].

CLASSIFICATION OF SCARS:

Fine line scars: Eg: surgical scars.

Wide stretched scars: Eg: Abdominal striae of pregnancy.

Atrophic scars: Eg. Chicken pox scars.

Scar contractures: Eg. Burn injury.

Raised skin scars:

A) Hypertrophic scars – raised scars that remain within the boundaries of the wound.
B) Keloidal scars – raised scars that spread beyond the boundaries of the wound.

Intermediate scars: scars which are difficult to categorize[2]

KELOID:

DEFINITION:

A keloid may be defined as a benign growth of fibrous tissue developing from an abnormal healing response to a cutaneous injury, extending beyond the original borders of the wound or inflammatory response[3].

EPIDEMIOLOGY:

INCIDENCE: The epidemiology of keloids is variable. The reported incidence in the general population ranges from a high of 16%[4] in Zaire among adults to a low of 0.09% in England[4].

AGE AND SEX DISTRIBUTION: Keloids are more common in the age group of 10 to 30 years[5]. Mean age of keloid diagnosis in males is 22.8 years and in females is 22.3 years. Sex incidence is equal[5].

HISTORY:

Keloids were first described in an Egyptian papyrus[6] about 1700 b.c. Jean Louis Alibert[6] (1768-1837) described these lesions in 1806 and called them “cancroide”. To avoid confusion with cancer, he changed the name to “cheloide”. The word is derived from the Greek “chele” meaning “crab’s claw” and the suffix “oid” meaning “like”.

Yorubas[6], a tribe from Nigeria had the custom of facial markings and ear piercing .They described the familial occurrence of keloids as early as 800a.d.The Olmec tribe of Mexico[6] in pre – Columbian times used keloid scarification as a means of decoration. The women of Nubia-kush in Sudan are intentionally scarified with facial keloids as a means of decoration.

ETIOLOGY:

The predisposing factors include: a) Trauma b) Skin tension c) Infection d)Autoimmune phenomenon e) Hormonal factors f) Genetic factors f)Drugs g) Foreign material h) Racial factors i)Climate

TRAUMA: It is an important provoking factor. The following types of trauma have been implicated in the development of keloids. Incisions, abrasions, insect bites, chemical and thermal burns, scalds, vaccination (BCG& varicella)[7], ear lobe piercing[8], circumcision[9] , coronary artery bypass surgery, waxing[10], umbilical keloid [11] following cord separation, corneal keloid[12] following surgery, intraoral keloid[13] as a complication of forehead flap in the oral cavity, palmar keloid following release operation for Dupuytren's contracture[14,15].

INFECTION: Infections like folliculitis, small pox, chicken pox[16], may act as a precipitating factor for keloid formation. Some types of keloid are more prone for suppuration called as suppurative keloidosis[17,18].

SKIN TENSION: There are 2 contradictory theories explaining the role of skin tension in the development of keloid. One school of thought says that in areas of increased skin tension like the chest and the back, the prevalence of keloids is higher. Another theory proposed,contradicts the aforementioned one. It states that ear,inspite of having low skin tension has high prevalence of keloids. So the role of skin tension in keloid pathogenesis is not clearly defined yet. It has been observed that high tension is present in the edges and not in the centre of keloids. So healing easily takes place in the centre and not in the edges. And the expansion of keloids is in the direction in which it is pulled[19].

AUTOIMMUNE PHENOMENA: Following trauma, sebum is secreted intradermally. This sebum acts as an antigen to trigger an autoimmune granulomatous response. This is called sebum autoimmune hypothesis[20].

HORMONAL FACTORS: Keloids exhibit a higher level of androgen binding than surrounding normal tissues[23]. Upper chest, back are predisposed to keloid formation as they have a higher rate of dihydrotestosterone metabolism. So it is suggested that topical anti-androgens may play a role in therapy. Keloids are found to be associated with acromegaly, pregnancy[21], hyperthyroidism[22]. This further supports the view that hormones are involved.

GENETIC FACTORS: Autosomal dominant inheritance with incomplete penetrance and variable expression[24] has been suggested. Autosomal recessive inheritance has also been described. HLA associations include HLA B14, HLA B21, HLA DR5, HLA DQW3[25]. Heterogeneity in the chromosomal loci 2q23 and 7p21 has been suggested. Patients with blood group A have increased tendency to form keloids[38].

FOREIGN MATERIAL: Presence of foreign material either exogenous (suture material) or endogenous (embedded hair) may lead to keloid formation.

DRUGS: In athletes taking anabolic steroids, linear keloids[26] have been reported. Isotretinoin given after dermabrasion or argon laser for acne or rosacea may delay wound healing and cause keloids[27].

RACIAL FACTORS: More common in blacks, Chinese, Afrocarribeans[5]. Blacks: Whites ratio is 15:1. This may be due to increased melanocyte stimulating hormone which can lead to keloid formation.

CLIMATE: Europeans living in tropics form keloids more frequently than those living in temperate zones. This may suggest a role for climate in the etiology of keloids[28]

PATHOGENESIS:

The pathogenesis of keloid is complex. The balance between collagen synthesis and degradation is maintained by matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. This in turn is controlled by TGF - β. TGF- β is of three types 1, 2, 3. Increased levels of types 1& 2 lead to keloid formation as it inhibits MMP'S and potentiates TIMP'S.TGF –β Type 3 is found to play a protective role antagonising the action of 1&2 types[1]. Mannose 6 phosphate also inhibits TGF-β types 1&2. There are various other studies which suggest a role for Plasminogen – Plasmin system[29] in the pathogenesis of keloid. Plasmin is found to activate TGF-β. Activin[30], another protein of the TGF -β superfamily stimulates the proliferation of fibroblasts and hence plays an important role. Cytokines like IL-6, TNF α , were found to be increased in keloids[31]. So cytokines are thought to play a part in the evolution of keloids.

Recently a new theory called as the neurogenic inflammation hypothesis[32] has been put forward. This states that mechanical stress stimulates nociceptors on sensory fibres in skin which release neuropeptides like substance P, CGRP, TGF -β which in turn activates fibroblasts.

CLINICAL FEATURES:

Within 3 to 4 months of a provocative stimulus, keloids develop. The lesions are firm, pink, or red plaques which continue to grow for months or even years, and extend beyond the margins of the original lesion. They may assume a dumb bell shaped configuration or become bizarre and irregular. In ears, pedunculated forms are seen. Consistency ranges from soft and doughy to hard. The lesions can also undergo suppurative necrosis[17,18]. It can rarely ulcerate. Malignant degeneration such as squamous cell carcinoma has also been reported in the literature, though extremely rare[33,99]. The sites of occurrence vary among different racial groups. In decreasing order of frequency, these are:

Whites: face (cheeks, earlobes), upper extremities, chest, neck, back, lower extremities, breast, abdomen.

Blacks: face, lower extremities, breast, chest, back, abdomen.

Other sites involved are: Genitals –following circumcision or trauma.

Cornea – following surgery or trauma.

Umbilicus – following cord separation.

Palms – following release operation for Dupuytren's

Contracture.

Symptoms commonly observed are: Pruritus (80%), pain (50%), burning sensation, limitation of movement (if present over joint).

HISTOPATHOLOGY OF KELOID:

Epidermis is normal. There is no scarring of papillary dermis. Collagen bundles or whorls of collagen with peripheral capsule like band are present. These are stretched and aligned in the same plane as the epidermis. The centre of the lesion is relatively acellular. The collagen fibres are large, thick and hyalinised. A horizontal fibrous band is seen in the upper reticular dermis. There is a tongue like advancing edge beneath a normal epidermis and papillary dermis, in contrast to hypertrophic scars in which there is no advancing edge[34].

BIOCHEMICAL CHARACTERISTICS:

Total collagen as measured by hydroxy proline estimation method is increased. Proteoglycan content measured by glucosamine estimation method is also found to be increased. Water content, measured as a difference between wet weight and dry weight of scar biopsies is found to be high in keloid. Keloids have higher acid collagen than pepsin soluble collagen. As pepsin soluble collagen represents cross linked collagen, cross linking is found to be defective in keloids[35].

DISTINGUISHING FEATURES:

FEATURE	NORMAL SCAR	HYPERTROPHIC SCAR	KELOID
PEAK AGE OF ONSET	Any age	Any age	10 -30 years
RISK FACTORS	None	Increased wound depth, size, tension, infection.	Dark skin, family history, blood group A, hormones, site of injury
EXTENSION	Never extends beyond margins	Never extends beyond margins	Extends beyond the margins
TIME OF ONSET	< 4 weeks	< 4 weeks	3 months to years
COURSE	Full Resolution	Partial resolution	No resolution
HISTOLOGY	No Myofibroblast, fine collagen.	Myofibroblast + , fine collagen	No Myofibroblast, thick collagen[36]

ASSOCIATIONS OF KELOID:

Dupuytren's contracture, Ehlers Danlos syndrome, Rubinstein Taybi syndrome, Dubowitz syndrome, Pachydermoperiostosis, Geominne syndrome, Turner's syndrome, Noonan's syndrome, Acne conglobata, Hidradenitis suppurativa, Pilonidal cysts, Pseudofolliculitis barbae[37].

DIAGNOSIS:

This is based on the typical morphology of the lesion. Histopathology and electron microscopic examination can be done in doubtful cases.

DIFFERENTIAL DIAGNOSIS:

Hypertrophic scar: Lesions do not extend beyond the margins of the wound, there is a tendency for spontaneous resolution, biopsy shows young thin collagen fibres, myofibroblasts are present.

Lobomycosis : Fungal infection caused by Lacacia loboi. Biopsy shows fungi, giant cells. Fungi are lemon shaped, joined to one another by a narrow tubular neck. The lesions are devoid of collagenous fibrosis.

Keloidal morphoea: Biopsy helps in differentiating the two. Thinned out epidermis, homogenised, hyalinised, hypertrophic collagen fibres are seen. The eccrine glands are seen high up in the dermis[40].

Dermatofibroma: The common site of involvement is limbs. Dimple sign will be positive. In biopsies, epidermis is hyperplastic, Grenz zone is seen. In the dermis proliferation of histiocytes, giant cells are seen.

Dermatofibrosarcoma protruberans: Common in females. Rapid growth is seen. Usually occurs as an irregular plaque which later develops nodules.HPE shows a storiform arrangement of spindle shaped cells[42].

Keloidal granuloma faciale: More common in men. It is usually seen in the face as a reddish plaque with dilated follicular orifices. Biopsy shows a Grenz zone, and a vasculitic picture[41].

Keloidal sarcoidosis: Involvement of other systems should be looked for. Biopsy shows a naked granuloma with reticulin fibres. Asteroid and Schaumann bodies can be seen.

Lupus vulgaris: Can also present with a keloidal morphology. Biopsy shows the typical tuberculoid granuloma.

Erythema elevatum diutinum: This has a vasculitic picture on biopsy[39].

Corneal keloid: Has to be differentiated from corneal neurofibroma, recurrent limbal dermoid[12], corneal myxoma, corneal xanthoma.

MANAGEMENT OF KELOID:

It should be based on three pronged approaches. It includes

1. Manipulation of the mechanical properties of wound repair.
2. Correction of the abnormal balance of collagen synthesis and degradation.
3. Alteration of the immune inflammatory response.

PREVENTION:

1. Pre-surgical evaluation of potentially high risk patients by clinically evaluating their previous surgical scars
2. Family history of keloids should be looked for.
3. Non essential cosmetic surgeries should be avoided in patients who are prone to keloids.
4. Adequate precautions should be taken during surgery such as proper orientation of incision lines (parallel to skin creases) to reduce wound tension.
5. Incision sites in the mid-chest or over the joints should be avoided as far as possible.
6. Avoid the use of buried absorbable sutures, and use of non-absorbable sutures should be carried out.
7. Use of electrosurgical devices must be restricted.

Treatment modalities available are as follows:

1. Compression therapy[60,61].
2. Cryotherapy[63,64,65].
3. Intralesional therapies:
    a) Intralesional Triamcinolone acetonide[67,68,69,70].
    b) Intralesional 5- Fluorouracil[71,72,73,74]
    c) Intralesional Verapamil[75,76,77,78]
    d) Intralesional Interferons[81,82]
    e) Intralesional Bleomycin[79,80]
4. Silicone gel sheets[83,84].
5. Lasers :
    a) Pulsed dye laser[85,86]
    b) ND:YAG laser.[87,88]
    c) Co2 laser[90]
    d) Argon laser[89]
6. Surgical excision[95,100].
7. Combination therapies:
    a) Surgical excision can be combined with intraoperative and/or postoperative steroid injections[97].
    b) Surgical excision with postoperative Verapamil injections[77].
    c) Surgical excision followed by radiotherapy[96].

d) Intralesional 5- fluorouracil combined with Triamcinolone injection[102,103,104].

e) Cryotherapy followed by Intralesional Triamcinolone and silicone gel sheets[94].

8. Miscellaneous therapies:

a) Topical tamoxifen[43,44] – Nonsteroidal antiandrogen that decreases the expression of TGF- β.

b) Onion extract gel[45].

c) Retinoic acid[46,47] – reduction of fibroblast proliferation and collagen synthesis.

d) Putrescine [48]- inhibits tissue transglutaminase that plays a role in collagen crosslinking.

e) Tranilast[49]

f) Botulinum toxin[50].

g) Enalapril[51].

h) Pentoxiphylline

i) Colchicine.

j) Tacrolimus.

k) Alloderm[52](Acellular human dermis.)

l) Camptothecin [53] - inhibits collagen synthesis

m) Intralesional collagenase[54].

n) Quercetin[55].

o) Intralesional Etanercept[56].

p) Heparin[57].

q) Green tea[58].

r) Imiquimod[59].

s) Creams containing extracts from plants such as Bulbine frutescens and Centenella asiatica.

COMPRESSION THERAPY:

This includes

a) Button compression.

b) Pressure ear rings.

c) Elastic adhesive bandages.

d) Zinc oxide adhesive bandages[62]

MECHANISM OF ACTION:

It decreases oxygen tension through occlusion of small vessels and subsequent reduction in tissue metabolism, fibroblast proliferation and collagen synthesis.

Capillary pressure greater than 4mm Hg is applied for > 23.5 hours / day. This has to be continued for 6 to 12 months. The disadvantages are thermal insulation and movement restriction[60,61].

CRYOTHERAPY:

It is a common modality which is used to treat hypertrophic scars and keloids. Substances which are used in cryotherapy are

a) Liquid nitrogen - - 196 degree Celsius.
b) Ice - 0 degree Celsius
c) Co2 slush - - 20 degree Celsius
d) Co2 snow - -79 degree Celsius
e) Nitrous oxide - -90 degree Celsius

MECHANISM OF ACTION:

Destruction of keloidal fibroblasts by

a) Intracellular and extracellular ice formation.
b) Osmolarity changes.
c) Apoptosis.
d) Thermal shock.
e) Vascular changes.
f) Coagulation of proteins.
g) It also causes local edema and gives anaesthetic effect for subsequent injection of intralesional steroids.

Macroscopic changes observed after cryotherapy are that, during and immediately after the application, white ice field is formed. A minute

later, after thawing a purplish violet colour develops at periphery and moves centrally. And the deeper tissues become pale. In one or two days a hemorrhagic blister on an erythematous base develops in the centre. In a week, blister forms an eschar. Eschar separates spontaneously in 2 weeks.

SIDE EFFECTS:

Acute : pain, headache, edema, blister, fever, syncope.

Chronic : hypopigmentation, depigmentation, hyperpigmentation, milia, arthralgia, nerve damage, paraesthesia, atrophy[63,64,65].

TECHNIQUES AVAILABLE:

a) Cryospray
b) Cryoroller.
c) Cryoprobe.
d) Intralesional cryosurgery[66].

INTRALESIONAL CORTICOSTEROID INJECTION:

It is very widely used in the treatment of keloids. The preferred steroid is Triamcinolone acetonide. And it is used in a concentration of 10 to 40 mg/ ml, depending on the size and location of the lesion.

METHOD OF ADMINISTRATION:

Triamcinolone acetonide 40 mg/ ml is injected alone or in combination with lignocaine 1%, with a 25 to 27 gauge needle attached to an insulin syringe. The needle is introduced into the lesion at an angle of 30 to 45 degrees with bevel of the needle pointing downwards. Inject only after aspiration.0.05 to 0.1ml is injected at each site sequentially by multiple puncture technique, so as to cause blanching. Blanching should not be allowed to spread to the adjacent tissue. Pressure hemostasis is achieved and dressing with antibiotic ointment is given. Postoperatively antibiotics, analgesics, and anti- inflammatory drugs are given. The injections are given at intervals of 3 to 4 weeks.

MECHANISM OF ACTION:

a) Inhibits fibroblast growth.
b) Inhibits collagen and glycosaminoglycan synthesis.
c) Decreases TGF-β and increases basic- FGF production.
d) Decreases the release of inflammatory mediators.
e) Decreases alpha 2 macroglobulin levels (which inhibits collagenase).
f) Vasoconstrictive effect[67,68,69,70]

SIDE EFFECTS:

a) Pain during injection.

b) Skin atrophy.

c) Depigmentation, hypopigmentation

d) Telangiectasia.

e) Necrosis and ulceration (rare)

f) Cushingoid symptoms[98] (rare)

INTRALESIONAL 5 – FLOUROURACIL:

It is a pyrimidine analogue.

MECHANISM OF ACTION:

Inhibiting DNA synthesis by competing with Uracil incorporation. It is postulated that it acts on fibroblasts and decreases its proliferation.

METHOD OF ADMINISTRATION:

5 – Flourouracil is available in a concentration of 50 mg/ml. It is given intralesionally alone or in combination with 1% lignocaine with a 25 to 27 gauge needle attached to an insulin syringe. 0.05 to 0.1 ml is given at each site sequentially by multiple puncture technique to cover the the entire lesion. The injections are given at an interval of 1 or 2 weeks. In a single session, not more than 2ml should be given.

CONTRAINDICATIONS:

Pregnancy, lactation, infection, bone marrow suppression, liver and kidney disease.

SIDE EFFECTS:

Pain, burning sensation, ulceration, hyperpigmentation, necrosis[71,72,73,74].

INTRALESIONAL VERAPAMIL INJECTION:

It is a calcium channel blocker.

MECHANISM OF ACTION:

They depolmerize actin filaments and alter the shape of fibroblasts from bipolar to spherical and thus results in increase in collagenase production[75,76,77,78].

METHOD OF ADMINISTRATION:

It is available in a concentration of 2.5mg/ml. It is given with a 25 to 27 gauge needle attached to an insulin syringe. 0.05 to 0.1ml is given at each site sequentially, and the entire lesion is covered. The injections are given at intervals of 3 weeks.

CONTRAINDICATIONS:

Hypotension, left ventricular dysfunction, sick sinus syndrome, atrial fibrillation, or flutter.

ADVANTAGES:

Verapamil, being a solution is much easier to inject intralesionally. It has less side effects compared to triamcinolone[76].

INTRALESIONAL BLEOMYCIN:

It is a chemotherapeutic agent used in many cancers.

MECHANISM OF ACTION:

a) Blockage of cell cycle
b) Degrading DNA and RNA.
c) Production of reactive oxygen species

MODE OF ADMINISTRATION:

Bleomycin tattooing or multiple puncture technique is used. Multiple punctures are made in the lesion and 1.5 IU/ ml of bleomycin is applied topically to these areas. About 40 punctures / mm^2 are made. 3 to 5 infiltrations are given in one month period.

SIDE EFFECTS:

Pain, hyperpigmentation , ulceration[79,80].

INTRALESIONAL INTERFERONS:

Interferons alpha, beta, gamma can be used.

MECHANISM OF ACTION:

a) Increases collagenase activity.
b) Decreases fibroblast production of glycosaminoglycans.

MODE OF ADMINISTRATION:

It is given at a dosage of 1 million units/cm^2 of scar with a maximum of 5 million units. It is given 3 times per week for 3 weeks.

SIDE EFFECTS:

Influenza like symptoms, nausea, diarrhoea, hypotension, tachycardia, dysarrythmia[81,82].

SILICONE GEL SHEETS:

Silicones are synthetic polymers based on dimethyl siloxane monomer. They have a repeated structural unit Si0 $(CH_3)_2$. 3 types of silicones are used namely fluids, gels, elastomers.

MECHANISM OF ACTION:

It is postulated that it causes hydration and modulates the effect of keratinocytes on fibroblasts .Hydration is thought to result in decreased capillary activity with ultimate reduction in collagen deposition via decreased synthesis of pro -inflammatory cytokines. It is also thought to alter oxygen tension in tissues. Static electricity that develops at gel dressings and skin interface or the effect of temperature changes leads to blockage of growth factors which result in diminished fibroblast activity and collagen breakdown.

MODE OF USAGE:

The sheet is trimmed from the standard sized sheet, so that it matches the specific scar. The sheet should extend atleast one to one and half inches around the lesion for a better hold. It is directly applied over the lesion and kept in place with a micropore tape. It is worn for 8 hours per day. Each sheet will last for 28 to 30 days[83,84].

LASERS:

Lasers are also used in the management of keloids. The types of laser used are

a) Co2 laser (10,600nm)
b) Nd :YAG laser (1064nm)
c) Pulsed dye laser (585nm)
d) Argon laser (488nm)

PULSED DYE LASER:

It acts by selective thermolysis[85,86]. It is given in a dosage of 5 J/cm^2.

ND: YAG LASER:

It has been suggested that Nd:YAG laser cause inhibition of collagen production. Dosage is 1.1*10^3 J /cm^2. The disadvantage is that melanin in epidermis causes most of the laser energy to be absorbed at superficial

level, so little or no effect is seen on deeper tissues. Recurrence rate is between 53 – 100%[87,88].

ARGON LASER:

It acts through photothermolysis. Has high level of recurrence (45 – 93%)[89].

CO2 LASER:

Superpulsed CO2 laser energy can stimulate the release of basic –FGF and inhibits release of TGF- β in both normal and keloid cells. It is used in a dosage of 2.5 W /$cm^{2.}$ It has a high level of recurrence that varies between 25- 74%[90].

SURGICAL EXCISION:

Surgical excision of keloid can either be done as keloid fillet flap method or keloid core excision[95,100]. It can also be combined with other modalities like intralesional triamcinolone[97] or verapamil[77] or along with radiotherapy[96].

COMBINATION THERAPIES:

When compared to a single modality of treatment combination therapies are found to be very useful in the treatment of keloid. Intralesional triamcinolone and 5 – fluorouracil can be combined together and given once in 3 weeks. This gives a faster response when compared to

5 – fluorouracil given alone and also the side effects of 5 – FU can be avoided by this technique[94].

Cryotherapy when combined with intralesional steroids aids in easy penetration of the drug due to the edema and also has a local anaesthetic effect for subsequent steroid injections.

Silicone gel sheets when combined with intralesional steroid injections were found to result in faster resolution of the scar[102,103,104].

AIM OF THE STUDY:

The aim of the study was

1. To study the efficacy of various modalities of treatment and to compare them with one another.
2. To study the adverse effects of the various modalities used.
3. To study the correlation between treatment response and the duration, size, number of lesions.

The different modalities of treatment used in this study were

1. Intralesional Triamcinolone (40mg/ml)
2. Intralesional 5-Flourouracil (50mg/ml)
3. Intralesional Verapamil(2.5mg/ml)
4. Combination of Intralesional Triamcinolone (40mg/ml)and Intralesional 5- Fluorouracil (50mg/ml)
5. Combination of Cryotherapy, Intralesional Triamcinolone and Silicone gel sheets.

MATERIALS AND METHODS:

Study design: Prospective randomized open labelled clinical trial.

Patients presenting with keloid to the dermatology department of our hospital during the study period of August 2008 to August 2010 were recruited. A diagnosis of keloid was made on clinical grounds and biopsy. A thorough history with regard to the onset of the lesion and whether it was spontaneous or followed acne, folliculitis, insect bite, varicella, trauma, surgery was taken to assess the etiology of the disease. The duration, progression of lesion, associated symptoms, family history were also asked for. The patients were also enquired about past history of thyroid disease and drug intake (retinoids, anabolic steroids) prior to the onset of the lesions.

A meticulous general and systemic examination was performed to look for associations. Complete dermatological examination was carried out. The site, number, size, consistency, colour of the lesions were noted. Care was taken to look for associated skin lesions.

A complete hemogram, liver function tests, renal function tests, blood group was done in all the cases. ECG and ECHO were done and cardiology opinion was obtained in patients who were to be started on injection Verapamil.

INCLUSION CRITERIA:

1. Age group 10- 60 years.
2. Both sexes.
3. Size of keloid between 1- 15 cm
4. Duration of less than 15 years.

EXCLUSION CRITERIA:

1. Pregnancy
2. Lactation
3. Heart disease.
4. Liver and kidney disease
5. Immunocompromised patients
6. H/O previous treatment

Patients were allocated to each group by simple randomisation. Clinical assessment of the scars was performed at the beginning of the study, and at every three weeks interval after starting treatment. The drugs were administered till the scars flattened or for a maximum period of 18 weeks whichever was earlier.

GROUP 1: Patients submitted for Intralesional Triamcinolone acetonide (40mg/ml):

Fifteen patients comprising the first group were treated with injection Triamcinolone acetonide 40mg/ml, with a 27 gauge needle attached to an insulin syringe. 0.2 ml was injected in each site ($1cm^2$), so as to cause blanching. The injection was given segment wise sequentially by multiple puncture technique so as to cover the entire lesion. Care was taken not to cause blanching of the surrounding area. Pressure hemostasis was obtained and antibiotic dressing was done. The patients were given injections at 3 weeks interval, till the flattening of the scar or for a maximum period of 18 weeks.

GROUP 2: Patients submitted for Intralesional 5- Fluorouracil injection (50mg/ml):

Fifteen patients comprising the second group were treated with injection 5- Fluorouracil 50mg/ml with a 27 gauge needle attached to an insulin syringe. 0.2ml was given at each site ($1cm^2$), sequentially by multiple puncture technique so as to cover the entire lesion. The injections were given at intervals of 2 weeks till the flattening of the scar or a maximum period of 18 weeks.

GROUP 3: Patients submitted for Intralesional Verapamil (2.5mg/ml) injection:

Fifteen patients comprising the third group were treated with injection Verapamil 2.5mg/ml with a 27 gauge needle attached to an insulin syringe. 0.2ml was injected at each site ($1cm^2$), sequentially, and the entire lesion was covered. The injections were given every 3 weeks till the resolution of the lesions or a maximum duration of 18 weeks.

GROUP 4: Patients submitted for combination of injection 5 –Flourouracil (50mg/ml) and injection Triamcinolone (40mg/ml):

Fifteen patients comprising the fourth group were treated with intralesional injection of 0.9ml of 5- Fluorouracil (50mg/ml) combined with 0.1ml of injection Triamcinolone (40mg/ml). 0.2ml of the combination was injected in each site ($1cm^2$) sequentially with multiple puncture technique. The injections were given at intervals of 3 weeks till the lesions flatten or for a maximum of 18 weeks.

GROUP 5: Patients submitted for Cryotherapy followed by Intralesional Triamcinolone (40 mg/ml) combined with Silicone gel sheet application:

Fifteen patients comprising the fifth group were initially treated with Cryotherapy using liquid nitrogen applied by a cotton tipped wooden stick for a period of 20 to 30 seconds. A single freeze thaw cycle was applied.

This was followed by injection of 0.2 ml of Triamcinolone acetonide(40mg/ml) at each site ($1cm^2$) sequentially to cover the entire lesion. Silicone gel sheets were applied over the lesions and kept in place by a micropore tape. The patient was advised to keep the sheet in place for 8 hours per day. The injections were given at 3 weeks interval till the scar flattens or a maximum period of 18 weeks.

The clinical assessment of the scar was done based on Vancouver [101]scar scale which was modified as scar vascularity could not be assessed due to lack of resources. The other parameters of the scar scale like pigmentation, pliability, height were assessed every three weeks.

PIGMENTATION:

0 - Normal

1 - Hypopigmentation

2 - Mixed

3 - Hyperpigmentation

PLIABILITY:

0 - Normal

1 - Supple (flexible with minimal resistance)

2 - Yielding (giving way to pressure)

3 - Firm (inflexible, resistant to manual pressure)

4 - Banding (rope like tissue that blanches)

5 - Contracture (permanent shortening of scar producing deformity)

HEIGHT:

0 - Normal

1 - < 2mm

2 - 2 to 5 mm

3 - > 5mm

Itching which is an important symptom in keloid was also assessed. The scale for self assessment of itching is as follows:

0 - No itchy sensation

1 - Sometimes itchy

2 - moderately itchy , tolerable.

3 - Severe intolerable constant itching

The complications of therapy like

a) Atrophy
b) Hypopigmentation
c) Hyperpigmentation
d) Depigmentation
e) Telangiectasia
f) Necrosis
g) Ulceration
h) Blistering
i) Pain and burning sensation were noted in each visit.

STATISTICAL ANALYSIS:

The sample size for this study was calculated to be 15 in each group. For each study parameter, in each group, the mean value was calculated. Non parametric repeated measures ANOVA test (Friedman test) was used for analysis. Kaplan Meier graphs and log rank test were done to compare the rate at which all the study parameters reduced to zero with the 5 modalities. Score 0 in each parameter was considered to be the complete response. To look for any significant association between the duration, size, etiology and number of lesions with treatment response (complete flattening), Fischer's exact test was used. A p value of less than 0.05 was considered to be statistically significant.

OBSERVATIONS:

An analysis of the clinical profile of the patients recruited for the study revealed the following data.

There were 38 males and 37 females in our study group.

The ages of the patients ranged between 10 to 60 years .The majority of the males were in the 20 to 30 years age group, and the females were most common in the 30 to 40 years age group

TABLE 1: AGE AND SEX DISTRIBUTION:

AGE GROUP / SEX	MALES	FEMALES	TOTAL
10-20 YEARS	4	10	14
21-30 YEARS	16	10	26
31- 40 YEARS	13	14	27
41-50 YEARS	1	2	3
51-60 YEARS	4	1	5
TOTAL	38	37	75

TABLE 2: ETIOLOGY OF KELOID:

ETIOLOGY	NUMBER
SPONTANEOUS	51
TRAUMA	11
ACNE VULGARIS	7
HERPES ZOSTER	3
SURGERY	2
TATOO	1

51 patients had spontaneous onset of keloids. A history of trauma prior to the onset of the lesions was obtained in 11 patients. 7 patients had acne as the preceding lesion.3 patients had keloids occurring at the site of herpes zoster scar. 2 of them had keloids developing at the site of previous surgical scar. Keloid occurred at the site of tattoo in a single patient.

The duration of the lesions ranged between 1 to 10 years in our study group. 20 patients had lesions of ≤ 1 year duration. Majority (37) had lesions of 2 to 4 years duration.18 patients had keloids ≥ 5 years duration.

A positive family history (8%) was obtained in 4 males and 2 females.

The number of keloids in each patient was also variable. 39 of them had a single lesion and 36 of them had multiple lesions. The number of keloids ranged between 1 to 22.

The size of the keloids was also assessed. The smallest was found to be 1 cm and the largest was found to be 13 cm. 43 patients had keloids of less than 5 cm and 32 of them had keloids more than 5 cm.

TABLE 3: SITES OF INVOLVEMENT:

SITES OF INVOLVEMENT	NUMBER
CHEST	38
SHOULDER	16
FOREARM	10
ARM	3
BACK	2
ABDOMEN	2
THIGH	1
NECK	1
HAND	1
LEG	1

The sites of involvement in the descending order of frequency was found to be chest (38), shoulder (16) , forearm (10) , arm (3) , back (2), abdomen (2), thigh (1),neck (1), hand (1), leg(1).

Blood group 0+ve was found to be the commonest in our patients. Diseases associated were Acne vulgaris, Pitryiasis versicolor and hirsuitism.

The distribution of keloids in each group according to the etiology, duration, number, size, and sites were found to be the following.

TABLE 4: ETIOLOGY OF SCARS IN EACH GROUP:

ETIOLOGY/GROUPS	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
SPONTANEOUS	10	11	12	11	7
ACNE	2	-	2	-	3
TRAUMA	2	4	1	1	3
SURGERY	1	-	-	1	-
HERPES ZOSTER	-	-	-	2	1
TATOO	-	-	-	-	1

This table depicts the cause of keloid in each group. This shows that the majority were spontaneous in onset in each group.

TABLE 5: DURATION OF KELOID IN EACH GROUP:

DURATION IN YEARS	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
≤ 1 YEAR	4	1	3	4	6
2- 4YEARS	8	9	10	5	7
≥ 5 YEARS	3	5	2	6	2

TABLE 6: NUMBER OF KELOIDS IN EACH GROUP:

NUMBER OF KELOIDS	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
SINGLE	8	9	8	6	8
MULTIPLE	7	6	7	9	7

TABLE 7: SIZE OF KELOIDS IN EACH GROUP:

SIZE IN CM	GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
≤5CM	9	8	9	8	9
>5CM	6	7	6	7	6

TABLE 8: SITES OF KELOID IN EACH GROUP:

SITE	**GROUP 1**	**GROUP 2**	**GROUP 3**	**GROUP 4**	**GROUP 5**
CHEST	9	6	6	8	9
THIGH	-	-	-	-	1
SHOULDER	2	3	6	3	2
FOREARM	3	2	1	2	2
ARM	-	2	1	-	-
BACK	1	-	1	-	-
ABDOMEN	-	-	-	1	1
NECK	-	1	-	-	-
HAND	-	1	-	-	-
LEG	-	-	-	1	-

OBSERVATIONS OF THERAPEUTIC RESPONSES:

GROUP 1: RESULTS OBTAINED IN PATIENTS TREATED WITH INTRALESIONAL TRIAMCINOLONE (40 MG/ ML) INJECTION:

PARAMETER/ NO OF WEEKS	0	3	6	9	12	15	18
PIGMENTATION	2.73	2.33 (>0.05)	1.73 (<0.001)	1.46 (<0.001)	1.26 (<0.001)	1 (<0.001)	0.93 (<0.001)
PLIABILITY	3	2.26 (>0.05)	1.67 (<0.01)	1.2 (<0.01)	0.73 (<0.001)	0.6 (<0.001)	0.4 (<0.001)
HEIGHT	2.46	2.2 (>0.05)	1.73 (>0.05)	1 (<0.001)	0.6 (<0.001)	0.4 (<0.001)	0.26 (<0.001)

Note: The mean values of each parameter are depicted in this table, and the p values are shown in the bracket.

NUMBER OF WEEKS/ PARAMETERS	PIGMENTATION	PLIABILITY	HEIGHT
3	-	6.67%	-
6	6.67%	6.67%	6.67%
9	6.67%	40%	26.67%
12	6.67%	53.33%	53.33%
15	13.34%	66.67%	66.67%
18	13.34%	73.33%	73.33%

This table shows the percentage of subjects who showed complete response at different weeks for each parameter studied.

There was a significant reduction in pigmentation (p value <0.001) by 6^{th} week. 13.34% of subjects showed complete response by 18^{th} week.

Pliability showed significant reduction by 6^{th} week (p value <0.01). 73.33% of subjects showed complete response by 18^{th} week. The median response time was found to be 12 weeks.

Significant reduction in height was seen by the 9^{th} week (p<0.001). 73.33% of the patients showed complete response by 18^{th} week. The median response time was 12 weeks. There was a significant reduction in itch (p <0.001) by the 3^{rd} week in this group.

The common side effects observed were hypopigmentation (14), atrophy (5), telangiectasia (5), pain (15).

GROUP 2: RESULTS OBTAINED IN PATIENTS TREATED WITH INTRALESIONAL 5 – FLOUROURACIL (50MG/ML):

PARAMETER/ NO OF WEEKS	**0**	**3**	**6**	**9**	**12**	**15**	**18**
PIGMENTATION	2.86	2.86 (>0.05)	2.6 (>0.05)	2.4 (<0.05)	2.2 (<0.001)	2.06 (<0.001)	2.06 (<0.001)
PLIABILITY	3	3 (>0.05)	2.33 (<0.05)	2 (<0.001)	1.8 (<0.001)	1.53 (<0.001)	1.4 (<0.001)
HEIGHT	2.4	2.4 (>0.05)	2.4 (>0.05)	2.13 (>0.05)	1.93 (>0.05)	1.4 (<0.01)	1.06 (<0.001)

Note: The mean values of each parameter are shown in the table, and the p values are depicted in the bracket.

NUMBER OF WEEKS/ PARAMETER	**PIGMENTATION**	**PLIABILITY**	**HEIGHT**
12	-	6.67%	7%
15	-	20%	20%
18	-	26.67%	26.67%

This table shows the percentage of subjects who showed complete response at different weeks for each parameter studied.

There was a significant reduction in pigmentation by 9 weeks. (p value <0.05). None of the patients showed complete response by 18th week.

A significant reduction in pliability was noted by 6 weeks (p value <0.05). Only 26.67% of the subjects showed complete response by 18 weeks.

Height showed significant reduction by 15 weeks (p value<0.01).Only 26.67% of the patients showed complete response by 18 weeks.

There was a significant reduction in itch (p <0.001) by the 15th week in this group.

Hyper pigmentation and pain were the most common side effects observed. It was seen in 14 patients. Burning sensation immediately after injection was seen in all the patients. The other commonly seen side effects were blistering of the lesions (10), necrosis (1), ulceration (3).

GROUP 3: RESULTS OBTAINED IN PATIENTS TREATED WITH INTRALESIONAL VERAPAMIL (2.5MG/ML):

PARAMETER/ NO OF WEEKS	0	3	6	9	12	15	18
PIGMENTATION	3	2.93 (>0.05)	2.46 (<0.05)	2.13 (<0.001)	1.86 (<0.001)	1.8 (<0.001)	1.6 (<0.001)
PLIABILITY	3	2.53 (>0.05)	2.06 (<0.001)	1.8 (<0.001)	1.33 (<0.001)	0.86 (<0.001)	0.33 (<0.001)
HEIGHT	2.26	2.26 (>0.05)	2.06 (>0.05)	1.73 (>0.05)	1.13 (<0.001)	0.86 (<0.001)	0.53 (<0.001)

Note: The mean values of each parameter are shown in the table and the p values are noted in the brackets.

NO OF WEEKS/ PARAMETER	PIGMENTATION	PLIABILITY	HEIGHT
12	-	6.67%	6.67%
15	6.67%	26.67%	26.67%
18	6.67%	53.34%	53.34%

This table shows the percentage of patients who showed complete response at different weeks for each parameter studied.

There was a significant reduction in pigmentation by 6^{th} week (p value <0.05) 6.67% of the subjects showed complete response by 18^{th} week.

Significant reduction in pliability was noted by 6^{th} week (p value <0.001). 53.34% of the patients showed complete response by 18 weeks. The median response time was found to be 18 weeks.

Height showed significant decrease by 12^{th} week($p<0.001$). 53.34% of the patients showed complete response by 18^{th} week. The median response tine was found to be 18 weeks.

There was a significant reduction ($p< 0.001$) in itch by the 3^{rd} week.

Pain was the only untoward effect observed in this modality of treatment. It was seen in 8 patients.

GROUP 4: RESULTS OBTAINED FROM PATIENTS TREATED WITH A COMBINATION OF 0.9ML OF INJECTION

5-FLOUROURACIL (50MG/ML) AND 0.1ML OF INJECTION TRIAMCINOLONE ACETONIDE (40MG/ML):

PARAMETERS/ NO OF WEEKS	**0**	**3**	**6**	**9**	**12**	**15**	**18**
PIGMENTATION	2.93	2.6 (>0.05)	2.13 (<0.01)	1.73 (<0.001)	1.46 (<0.001)	1.13 (<0.001)	1.13 (<0.001)
PLIABILITY	3	2.46 (<0.05)	1.93 (<0.01)	1.35 (<0.001)	0.66 (<0.001)	0.4 (<0.001)	0.4 (<0.001)
HEIGHT	2.4	2.4 (>0.05)	2.06 (<0.05)	1.46 (<0.05)	0.66 (<0.001)	0.6 (<0.001)	0.4 (<0.001)

Note: The mean values of each parameter are shown in the table and the p values are depicted in the bracket.

NO OF WEEKS/ PARAMETERS	PIGMENTATION	PLIABILITY	HEIGHT
9	-	7%	7%
12	6.67%	60%	60%
15	13.34%	66.67%	66.67%
18	13.34%	66.67%	66.67%

This table shows the percentage of patients who showed complete response at different weeks for each parameter studied.

There was a significant reduction in pigmentation by the 6^{th} week (p value <0.01). 13.34% of the patients showed complete response by 18 weeks.

Pliability showed significant reduction by the 3^{rd} week (p value <0.05). 66.67% of the patients showed complete response by 18 weeks. The median response time was found to be 12 weeks.

Significant reduction in height was seen by the 6^{th} week (p value < 0.05). 66.67% of the patients showed complete response by 18 weeks. The median response time was calculated to be 12 weeks. There was significant reduction in itch (p <0.001) by the 3^{rd} week.

The side effects were atrophy in 2 patients, hypopigmentation and pain in 14 patients. Telangiectasia was seen only in one patient.

GROUP 5: RESULTS OBTAINED WITH PATIENTS TREATED WITH A COMBINATION OF CRYOTHERAPY, INTRALESIONAL TRIAMCINOLONE ACETONIDE (40MG/ML) AND SILICONE GEL SHEETS:

PARAMETERS/ NO OF WEEKS	**0**	**3**	**6**	**9**	**12**	**15**	**18**
PIGMENTATION	3	2.46 (<0.05)	2.06 (<0.001)	1.6 (<0.001)	1.26 (<0.001)	1.13 (<0.001)	1 (<0.001)
PLIABILITY	3	2.26 (<0.01)	1.8 (<0.001)	1 (<0.001)	0.33 (<0.001)	0.2 (<0.001)	0.2 (<0.001)
HEIGHT	2.46	2 (>0.05)	1.6 (<0.001)	0.73 (<0.001)	0.46 (<0.001)	0.266 (<0.001)	0.2 (<0.001)

Note: The mean values of each parameter are shown in this table and the p values are shown in the bracket.

NO OF WEEKS/ PARAMETERS	**PIGMENTATION**	**PLIABILITY**	**HEIGHT**
9	-	26.67%	33.33%
12	-	73.33%	60%
15	6.67%	80%	80%
18	20%	80%	80%

This table shows the percentage of subjects who showed complete response at different weeks for each parameter studied.

There was a significant reduction in pigmentation by the 3rd week (p value <0.05). 20% of the patients showed complete response by18 weeks.

Significant reduction in pliability was noted by the 3rdweek (p value <0.01). 80% of the subjects showed complete response by 18 weeks. The median response time was found to be 12 weeks.

Height showed significant reduction by 6 weeks (p value <0.001).80% of the subjects showed complete response by 18 weeks. The median response time was found to be 12 weeks. There was a significant reduction in itch (p< 0.001) by the 3rd week.

Hypopigmentation and pain were seen in 14 patients, atrophy in 4 patients and telangiectasia in 3 patients.

PERCENTAGE OF PATIENTS WITH COMPLETE RESPONSE AT THE END OF THE STUDY PERIOD:

PARAMETER/ GROUPS	PIGMENTATION	PLIABILITY	HEIGHT
GROUP 1	13.34%	73.33%	73.33%
GROUP 2	-	26.67%	26.67%
GROUP 3	6.67%	53.34%	53.34%
GROUP 4	13.34%	66.67%	66.67%
GROUP 5	20%	80%	80%

This table shows the percentage of patients with complete response with respect to each parameter at the end of 18 weeks.

DISCUSSION:

GROUP 1: PATIENTS TREATED WITH INTRALESIONAL TRIAMCINOLONE ACETONIDE (40 MG/ML):

The therapeutic response in each parameter has been assessed. The study done by Margaret Shanthi et al[76] showed a significant reduction in pigmentation by the 3rdweek. There was a significant change in pigmentation by the 6th week and 13.34% (2) of the patients showed complete response by 18 weeks in our study.

The study conducted by Manuskiatti [91]et al showed a significant change in pliability by 8 weeks and the study by Margaret Shanthi [76]et al had shown a significant change in pliability as early as 3 weeks. There was a significant change in pliability by 6th week in our study. The median response time was found to be 6 weeks in the study conducted by Margaret Shanthi [76]et al when compared to our study where it was found to be 12 weeks. 73.33% (11) of the patients had shown complete response by 18 weeks in our study.

The study conducted by Darougheh A [92]et al has shown that only 20% of the patients showed complete flattening by 12 weeks. Another study conducted by Muneuchi G [68]et al shows complete response in 40% of the patients. Layton AM and Yip J[63] et al had shown complete response in 85% of the patients, in concordance with our study.73.33% (11) of the

patients had shown complete flattening by 18 weeks in our study. The study conducted by Manuskiatti [91]et al showed significant flattening by the 8th week, which is in concordance with our study where significant flattening was achieved by the 9th week. The median response time in the study conducted by Margaret Shanthi et al[76] was found to be 6 weeks, when compared to our study where it was 12 weeks. The variation of the results in our study may be attributed to the fact that patients with family history of keloids, keloids of more than 5 years duration, size more than 10 cm were not included in the study conducted by Margaret Shanthi[76] et al. And it has been shown by previous studies that keloids of longer duration had delayed response to treatment.

Adverse effects like hypopigmentation were noted in 14 patients (93.33%). This is significantly higher than that seen in the study conducted by Manuskiatti [91]et al where it was 20%. The other untoward effects seen were atrophy (33.33%), telangiectasia (33.33%). Manuskiatti [91]et al had recorded atrophy and telangiectasia in 20% of his patients treated with Triamcinolone acetonide. Pain was noted in all the patients, similar to the study conducted by Manuskiatti[91] et al. Of the 15 patients in this group , 4 patients (26.67%) did not show complete flattening at the end of 18 weeks. 3 of the four patients had keloids of more than 1 year duration. Of all the other patients who showed complete response at 18

weeks, 2 had keloids of less than or equal to 1 year duration and 9 had keloids of more than 1 year duration.

3 out of 4 patients who did not show complete flattening at 18 weeks, had keloids of more than 5 cm size. But 3 patients with keloid of more than 5 cm size had shown complete response by 18 weeks.

5 out of 11 patients who had shown complete flattening had only a single keloid. The remaining 6 of them had multiple keloids. Among those who did not achieve complete flattening 2 had single keloid and 2 had multiple keloids.

Of the four patients who did not show complete flattening, 2 had spontaneous onset of keloids, and 1 patient had acne as the preceding lesion and the other had trauma preceding the onset of lesions. Of the subjects who showed complete flattening 8 had spontaneous of keloids, 1 had acne as the preceding lesion. Surgery and trauma preceded the onset of lesions in 1 patient each.

The site of involvement in 3 out of the 4 patients was the chest. Forearm was the site involved in the other patient. The patients who had shown complete response had sites of distribution as follows. Chest in 6, forearm in 2, shoulder in 2, upper back in 1 patient respectively.

GROUP 2: PATIENTS TREATED WITH INTRALESIONAL 5-FLOUROURACIL (50MG/ML):

In this study group none of them showed complete response with regard to pigmentation. A significant change in pigmentation was observed by the 9th week. None of the patients showed complete response by the end of 18 weeks also.

The study done by Manuskiatti[91] et al showed a significant reduction in pliability by 16 weeks when compared to our study where it was found to be 6 weeks. 4 out of 15 patients (26.67%) showed complete response in our study.

Manuskiatti et al[91] had shown a significant reduction in height by 8 weeks when compared to our study where it was achieved by 15 weeks. This may be due to the fact that weekly injections were given in the study in contrast to our study where the patients were treated with injections at 2 weeks interval. The study of Wu XL[93] et al showed complete flattening in 45.71% of the patients, when compared to our study where 26.67% (4 out of 15) of the patients showed complete response. This may be due to the fact that in that study biweekly injections of the drug were given. In our study, a time interval of 2 weeks between the injections was chosen as the incidence of side effects was found to be significantly higher, when the injections are given frequently, as observed in the earlier studies.

The occurrence of side effects was found to be severe in this treatment modality compared to the others. The study conducted by Kontochristopoulos[74] et al has shown that hyperpigmentation and pain after injection were seen in 100% of the patients. Hyperpigmentation in 14 patients (93.33%) and pain immediately after injection in 14 patients (93.33%) were observed in our study.

The study conducted by Manuskiatti[91] et al indicates burning sensation as an important adverse effect seen in all the patients. All the patients in our study complained of burning discomfort immediately after instillation of the drug. Blistering was seen in 10 patients (66.67%) in our study. The blisters appeared within 6 hours to 24 hours after the injection and burst spontaneously. It has also been observed that the incidence of blisters was more in the first two injections, and it decreased in subsequent injections. In the study of Fitzpatrick[72] et al ulceration was seen in 30% of the patients when compared to our study where it was observed in 20% of the patients (3). This could be attributed to the less frequent dosage in our study.

11 out of 15 patients (73.33%) did not show complete flattening of the lesion by 18 weeks. All the patients who had not shown complete flattening had keloids of more than 1 year duration. Among the 4 patients who showed complete flattening by 18 weeks, 3 of them had keloids of more than 1 year duration and 1 had keloid of ≤ 1 year duration.

5 of the 11 patients who did not achieve complete flattening had keloids less than or equal to 5cm and 6 of them had keloids of more than 5 cm.3 out of 4 patients who had complete flattening , had keloids ≤ 5cm and one patient had keloid >5cm.

In this group, all the 4 patients who had shown complete flattening had a single keloid. Out of the 11 patients who did not have complete flattening by the end of 18 weeks, 5 of them had a single keloid and the remaining 6 had multiple keloids.

The predisposing factors in these 11 patients were found to be trauma in 2, and spontaneous onset in the remaining 9 patients. Among the subjects who showed complete flattening by the end of 18 weeks, 2 had spontaneous onset and 2 of them had prior history of trauma.

The sites of involvement in these 11 patients were chest (3), shoulder (3), arm(2), forearm(1), hand(1), neck(1). Among the 4 patients who responded completely, 3 had lesions in the chest and 1 patient had lesion over the forearm.

GROUP 3: PATIENTS TREATED WITH INTRALESIONAL VERAPAMIL (2.5MG/ML):

The study conducted by Margaret Shanthi, Kalpana Ernest and Prema dhanraj[76] et al showed a significant reduction in pigmentation by the 9th week when compared to our study where it was achieved by 6 weeks. 6.67% (1) of the patients showed complete response with regard to pigmentation, in our study.

In the study of Margaret Shanthi[76] et al a significant change in pliability was seen in 3 weeks, when compared to our study where it was achieved by 6 weeks. 8 out of 15 patients (53.34%) showed a complete response by the end of 18 weeks in our study with respect to pliability. The study done by Margaret Shanthi [76]et al showed the median response time to be 9 weeks when compared to our study where it was recorded to be 18 weeks.

In the study conducted by Margaret Shanthi[76] et al a significant change in height was observed by 3 weeks when compared to our study where it was seen by 12 weeks. In the study conducted by Margaret Shanthi[76] et al the median response time was found to be 9 weeks, in contrast to our study where it was found to be 18 weeks. 8 patients (53.34%) showed complete flattening of the lesions by the end of 18 weeks in our study.

The variation of the results from the study of Margaret Shanthi [76]et al may be due to the following reasons. The exclusion criteria in their study were

patients with family history of keloids, darkly pigmented skin. The inclusion criteria in their study was patients with keloids of 2 to 10cm size, duration of less than 5 years, and cause of scar being trauma, surgery, insect bite , acne. In our study patients with family history, keloids of duration upto 15 years, size upto 15cm were included. Patients with spontaneous keloids were also included in our study. As it has been proved by earlier studies that keloids of longer duration are resistant to treatment, this might have had an influence in the treatment, in our study also.

On reviewing the side effects in the patients of this group, it was noted that pain was the only side effect noted. It was seen in 8 patients (53.33%). This is significantly lower when compared to the other treatment modalities. No other untoward effects were noted. This is in concordance to the study of Margaret Shanthi[76] et al.

46.66% (7) of the patients did not show complete flattening by the end of 18 weeks. Out of which 6 had keloids more than one year duration and 1 patient had keloid of ≤ 1 year duration. 2 of the 8 patients who had shown complete flattening by the end of 18 weeks, had keloids of ≤ 1 year duration, and the remaining 6 had keloids of more than a year duration.

4 out of the 7 patients who had not achieved complete flattening had keloids of size ≤ 5 cm and 3 had keloids of >5cm size. Among the patients who responded completely, 3 had size >5cm and 5 had size ≤ 5cm.

Of the 8 patients who had complete flattening by the end of 18 weeks, 6 had only a single keloid and 2 had multiple keloids. 5 patients who had multiple keloids and 2 of them who had a single keloid, did not achieve complete flattening by the end of 18 weeks.

5 of the 7 had spontaneous onset of keloids and history of acne preceding the onset of keloid was obtained in two patients. Of the 8 patients who had shown complete flattening by 18 weeks, 7 had spontaneous onset, 1 patient had prior history of trauma.

Arm(1) shoulder (2)and chest(3), back(1) were the sites of involvement in the 7 patients, who had not achieved complete flattening. The patients who showed complete flattening by 18 weeks had the following sites of involvement. Shoulder (4), Chest (3), forearm(1).

GROUP 4: PATENTS TREATED WITH A COMBINATION OF 0.9ML OF INTRALESIONAL 5 – FLOUROURACIL (50MG/ML) AND 0.1ML OF INTRALESIONAL TRIAMCINOLONE

(40MG/ML):

2 patients showed complete response in terms of pigmentation by the end of the study period. A significant change in pigmentation was noted by the 6^{th} week. 13.34% of the patients showed complete response by 18 weeks.

The study conducted by Manuskiatti [91]et al has shown a significant change in pliability by 8 weeks when compared to our study where it was seen by 3 weeks. This may be due to the fact that a lower concentration of Triamcinolone (20mg/ml) was used by them and the time interval between the doses was increased to 4 weeks in the last two treatments. 66.67% (10) of the patients showed complete response by 18 weeks and the median response time was found to be 12 weeks in our study.

The study of Asilian, Darougheh[92] et al showed complete response in 55% of the patients when compared to our study where 66.67% (10) of the patients had achieved complete flattening. The study by Manuskiatti [91]et al showed a significant change in height by 8 weeks when compared to our study where it was seen by 6 weeks. This may be due to the lower concentration of Triamcinolone used in their study and also the less

frequent dosing of once in 4 weeks for the last two treatments. The median response time was found to be 12 weeks in our study.

Regarding the side effects observed in this group, hypopigmentation and pain was noted in 14 patients (93.33%). Atrophy was seen in 2 patients (13.33%) and telangiectasia in 1 patient (6.67%). This is lower when compared to that observed in the patients treated with Triamcinolone alone.

33.33% of the patients did not show complete flattening by the end of 18 weeks. All the patients who had not shown complete flattening by 18 weeks had keloids of more than 1 year duration. 4 patients with duration of less than or equal to 1 year and 6 patients with keloid of more than 1 year duration showed complete flattening by the end of 18 weeks.

Considering the onset of keloids in these 5 patients, 4 had spontaneous onset and 1 patient had keloid developing at the site of previous surgical scar. 7 patients with spontaneous onset of keloids, 2 patients with keloids occurring at the involvement of herpes zoster lesions, 1 patient with a history of trauma prior to the onset of keloid showed complete flattening by the end of 18 weeks.

4 patients with keloid of size more than 5 cm size and one patient with keloid of less than 5 cm size did not show complete flattening by the end of 18 weeks. It was observed that 7 of the 10 patients who showed

complete flattening had keloids of less than 5 cm size and 3 of them had keloids of more than 5 cm size.

Out of the 10 patients who had shown complete flattening by 18 weeks, 5 had a single keloid and the remaining 5 had multiple keloids. 1 patient with single keloid did not show complete flattening by 18 weeks.4 of the remaining patients who had not shown complete flattening had multiple keloids.

4 patients who did not show complete flattening had keloid in the chest, and one had keloid over the shoulder. The sites of involvement in the subjects who showed complete flattening were as follows. Chest (4), shoulder (2), forearm(2), abdomen(1), leg(1).

GROUP 5: PATIENTS TREATED WITH CRYOTHERAPY, INTRALESIONAL TRIAMCINOLONE AND SILICONE GEL SHEETS:

Complete response with respect to pigmentation was seen in 3 patients. A significant change in pigmentation was seen in 3 weeks. 20% of the patients showed complete response by 18 weeks.

Complete response in terms of pliability was seen in 12 patients. A significant change in pliability was noted as early as 3 weeks. 80% of the patients showed complete response as early as 15 weeks. The median response time was found to be 12 weeks.

80% of the patients showed complete flattening of the lesion by 15 weeks. A significant change in height was noted by the 6^{th} week. The median response time was found to be 12 weeks.

The side effects observed were hypopigmentation in 14 patients (93.33%), Atrophy in 4 patients (26.67%), and telangiectasia in 3 patients (20%), pain in 14 patients.

In this group, 80% of the patients had shown complete response by 15 weeks. All the patients who had not shown complete flattening at 18 weeks had keloids of more than 1 year duration. Among the patients who had shown complete flattening at 18 weeks, 6 patients had keloids ≤ 1year and 6 patients had keloids of more than 1 year duration. All the three patients who had not shown complete flattening had keloids of size more than 5cm. Among the subjects who had shown complete flattening 9 of them had keloids of less than 5cm and 3 of them had keloids of size more than 5cm.

Out of the 12 patients who had shown complete flattening, 5 had only a single keloid and 7 had multiple keloids. Of the 3 patients who had not achieved complete flattening by the end of the study period, 2 had a single keloid and one person had multiple keloids.

Considering the etiology of keloids, 2 of the three patients had spontaneous onset of keloids and the other patient had keloid occurring at

the site of tattoo. Among the patients who had shown complete flattening, 5 of them had spontaneous onset of keloids, 3 of them had acne, 3 of them had trauma as the preceding event. One patient had keloid occurring at the site of previous herpes zoster lesion.

2 of the three patients who had not attained complete flattening by 18 weeks, had keloids in the chest and one patient had lesions over the forearm. 7 of the 12 patients who had shown complete flattening had lesions over the chest, 2 in the shoulder, and one each in the forearm, abdomen and thigh.

To sum up, comparison of the different parameters like pigmentation, pliability, height in the various treatment modalities shows that complete response in pigmentation was obtained in 20% of the patients in group 5, 13.34% of patients in group 4, 13.34% of patients in group 1and 6.67% of patients in group 3 by the end 18 weeks. None of the patients showed complete response in terms of pigmentation in group 2.

With regard to pliability 80% of the patients in group 5 had shown complete response by 15 weeks. 73.33% of the patients in group 1, 66.67% of the patients in group 4, 53.34% of the patients in group 3 and 26.67% of the patients in group 2 had shown complete response by 18 weeks.

With regard to height, 80%of the patients in group 5 had shown complete response by 15 weeks. 73.33% of the patients in group 1, 66.67% in group 4, 53.34% in group 3 and 26.67% in group 2 had shown complete response by 18 weeks.

There was a statistically significant reduction in itch by 3 weeks in all the groups except group 2 where there was a significant reduction only by 15 weeks.

The side effects were found to be severe in the group treated with 5-fluorouracil alone and were least in the group treated with Verapamil.

In the first group on comparing the treatment response in patients with keloids ≤ 1year with keloids of more than a year duration there is no statistically significant difference. (p=1.00).

In group 1 there is no statistically significant difference in the treatment response of keloids ≤ 5cm and keloids of more than 5 cm. (p=0.2352).

When the treatment response between single and multiple keloids are compared in the first group, no statistically significant difference is found. (p=1.00)

In group 1,when the treatment response between keloids of spontaneous onset and those due to other causes are compared , no statistically significant difference is found.(p=1.00)

In group 2, on comparing the treatment response in patients with keloids ≤ 1year and keloids of more than 1 year, no statistically significant difference is found. (p=0.2667).

In group 2, there is no statistically significant difference between keloids of size ≤5cm and keloids of more than 5cm (p=0.5692), regarding the treatment response.

When the treatment response between single and multiple keloids are assessed in group 2, no significant difference is found. (p=0.1033).

When the treatment response between keloids of spontaneous onset and those due to other causes are compared in this group, no statistically significant difference is found.(p=0.5165).

In group 3, when the treatment response is compared between keloids ≤1 year and keloids of more than a year duration no statistically significant difference is found. (p=1.00).

In the third group, there is no statistically significant difference between the treatment response in keloids ≤ 5cm and keloids of more than 5 cm size (p=1.00).

When the treatment response in patients with single and multiple keloids are compared in group 3, no statistically significant difference is found. (p=0.1319).

In group 3, when the treatment response between keloids of spontaneous onset and those due to other causes are compared, no statistically significant difference is found.(p=0.5692)

On assessing the treatment response in patients with keloids ≤1 year and keloids of more than a year duration in group 4, no significant difference is found (p= 0.2308).

In the fourth group, no statistically significant difference is found on comparing keloids of size ≤5cm and keloids of more than 5 cm size. (p=0.1189).

In the fourth group, no significant difference is found in the treatment response between single and multiple keloids. (p=0.5804).

In group 4, on comparing the treatment response in keloids of spontaneous onset and those due to other causes, no statistically significant difference is found. (p=1.00)

On comparing the treatment response in keloids ≤ 1year duration and keloids of more than a year duration in the fifth group, no statistically significant difference is found.(p=0.2286).

In the fifth group, no significant difference is noted in the treatment response between keloids ≤ 5cm and keloids of more than 5cm size. (p=0.2418).

No significant difference is noted in the treatment response between single and multiple keloids in group 5 (p=0.5692).

On comparing the treatment response in keloids of spontaneous onset and those due to other causes in the fifth group, no statistically significant difference is found (p=0.5692).

The best and earlier response (15 weeks) is seen in the group treated with a combination of Cryotherapy, Intralesional Triamcinolone acetonide and Silicone gel sheets. It has been found by earlier studies[106], that collagen breakdown by the steroid injection augments tissue polarization by the negatively charged static electric field on the silicone sheet. In a study by Eishi K et al[84], it has been observed that silicone gel sheets decrease the number of mast cells and increase the expression of Fas Ag by the lesional fibroblasts. This along with the action of Triamcinolone could have led to the faster resolution of keloids in this study group.

The group treated with 5- Flourouracil alone had shown the least response among the 5 study groups. A study conducted by Haurani et al[105] has shown that 5 – Flourouracil relies on thymidylate synthase activity to initiate apoptosis. And it has been shown that there is downregulation of apoptosis related genes in the keloid tissues[108], so this may result in a relative resistance to the medication. A study conducted by Kontochristopoulous[74] has shown that TGF – β expression is not

dramatically altered by 5 – Florouracil when compared to steroids. And the role of TGF – β in the pathogenesis of keloid is well known. All these factors could have led to the comparatively less response seen in this study group.

It has been observed that 73.33% of the patients treated with intralesional Triamcinolone acetonide alone and 66.67% of the patients treated with a combination of 5 – Flourouracil and Triamcinolone acetonide had shown complete flattening by 18 weeks. It has been observed that steroids increase b- FGF and decrease TGF- β[107].They also decrease the levels of IL- 1,6 which are known to be involved in keloid pathogenesis[31]. The number of mast cells and the release of histamine by mast cells is also decreased by steroids. But these factors are not altered by the use of 5-fluorouracil alone. This might have had an influence on the treatment response in our study as it is observed that the use of Triamcinolone alone or its combination with 5- Flourouracil produced better response compared to the use of 5 – fluorouracil alone.

CONCLUSION:

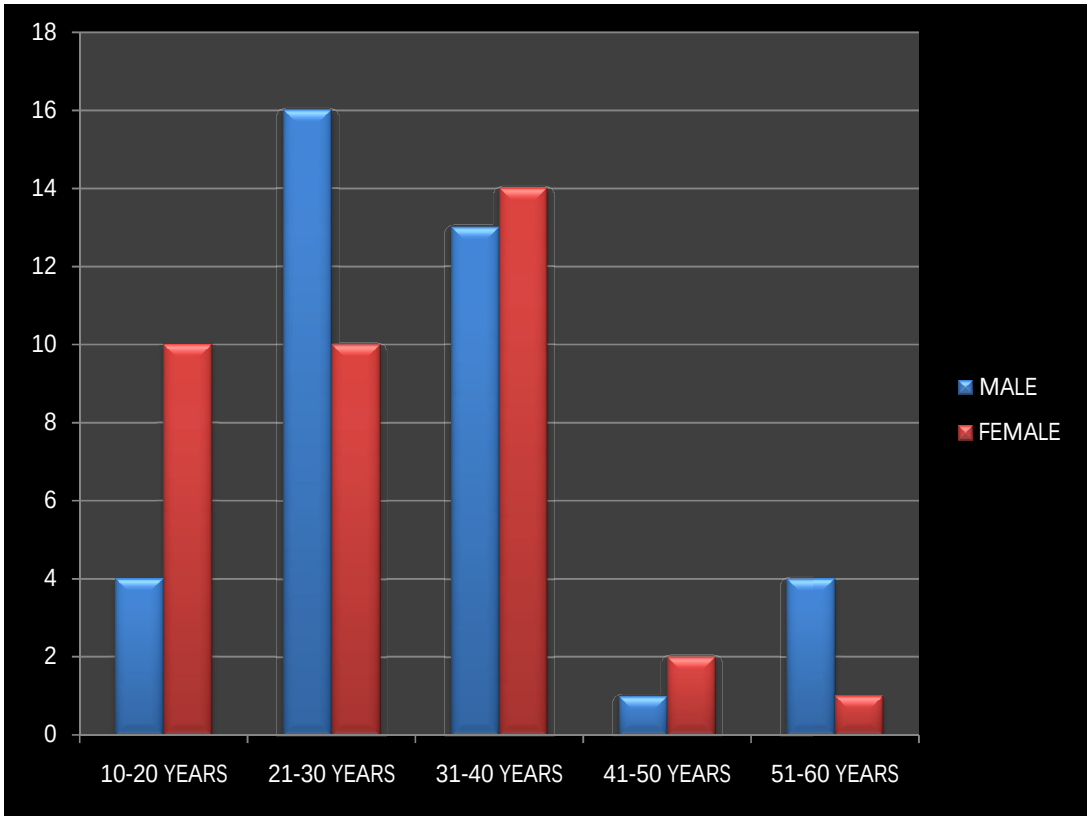
1. In our study the prevalence of keloids was found to be equal among both sexes.
2. The majority of keloids were seen in the 20 to 40 years age group in our study.
3. The maximum number (68%) of patients had spontaneous onset of keloids in our study. The other common risk factors observed were trauma, Acne vulgaris, herpes zoster, surgery, and tattoo in the descending order of frequency.
4. The most common site of occurrence of keloid in our study was observed to be the chest (50%). The other sites of involvement were shoulder, forearm, arm, back, abdomen, thigh, neck, hand and leg.
5. A positive family history was observed in 8% of the patients in our study.
6. The response to treatment varied between the study groups, for the three parameters assessed. **The patients treated with a combination of Cryotherapy, Intralesional Triamcinolone acetonide and silicone gel sheets showed the best and the earliest response, among all the 5 study groups (Pigmentation – 20%, Pliability and Height – 80%).**
7. **73.33% of the patients treated with Intralesional triamcinolone acetonide had shown complete response with respect to**

pliability and height. 13.34% of the patients had shown complete response to pigmentation in this group.

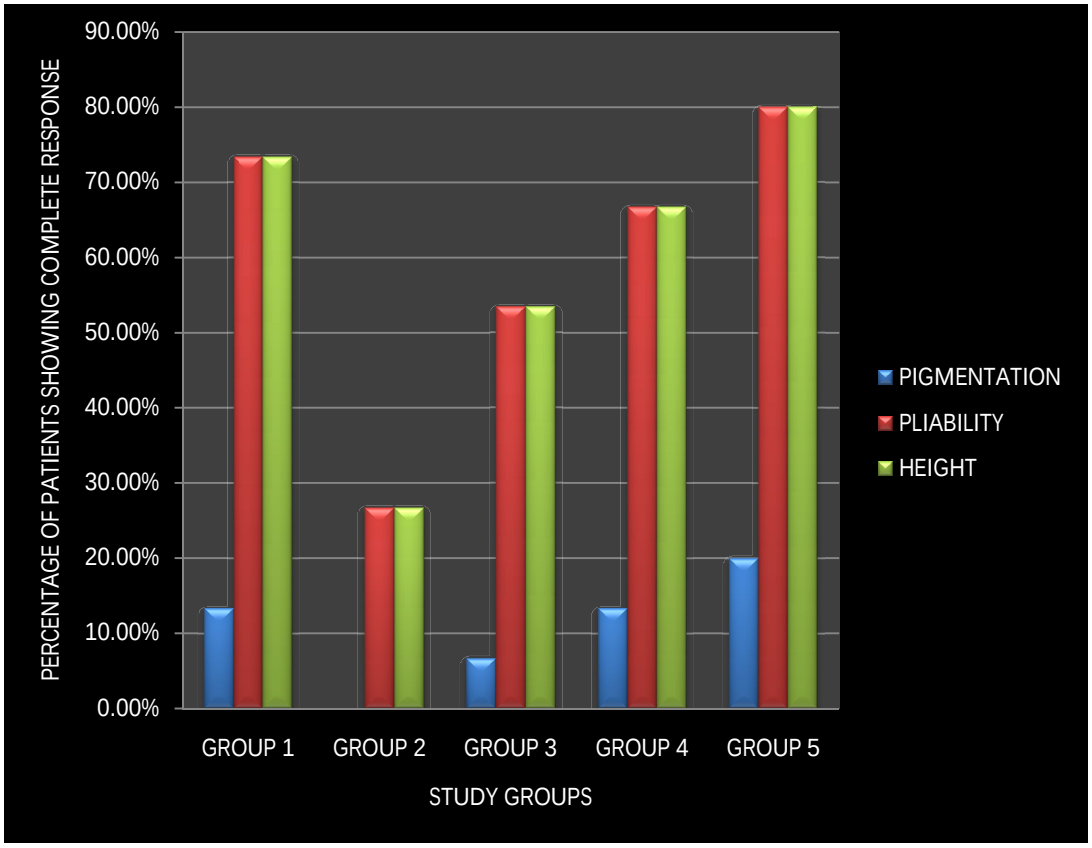
8. **Complete response was seen in 66.67% of the patients treated with a combination of Intralesional Triamcinolone Acetonide and 5 – Flourouracil with respect to pliability and height. 13.34% of the patients showed complete response to pigmentation in this study group.**
9. **In the group treated with Intralesional Verapamil, 53.34% of the patients had shown complete response in pliability and height. 6.67% of the patients showed complete response to pigmentation in this group.**
10. **The patients treated with Intralesional 5- Fluorouracil had shown the least response among all the 5 study groups. (Pigmentation – 0%, Pliability and Height – 26.67%).**
11. Itching was significantly reduced ($p<0.001$) in all the five modalities of treatment.
12. The side effects were severe in the group treated with 5- Fluorouracil alone and least in the group treated with Verapamil.
13. The number of keloids (single and multiple) in a patient does not significantly alter the treatment response in any of the study groups ($p > 0.05$).

14. There is no significant association between the size of the keloids and the response to therapy in any of the study groups ($p > 0.05$).
15. No significant association is observed between the duration of keloids ($\leq$ 1year and > 1 year) and the treatment response ($p > 0.05$). Each group in our study is comprised of 15 patients only. This remains the limitation of our study. Therefore studies in larger groups are needed to identify the influence of such factors on the treatment response.

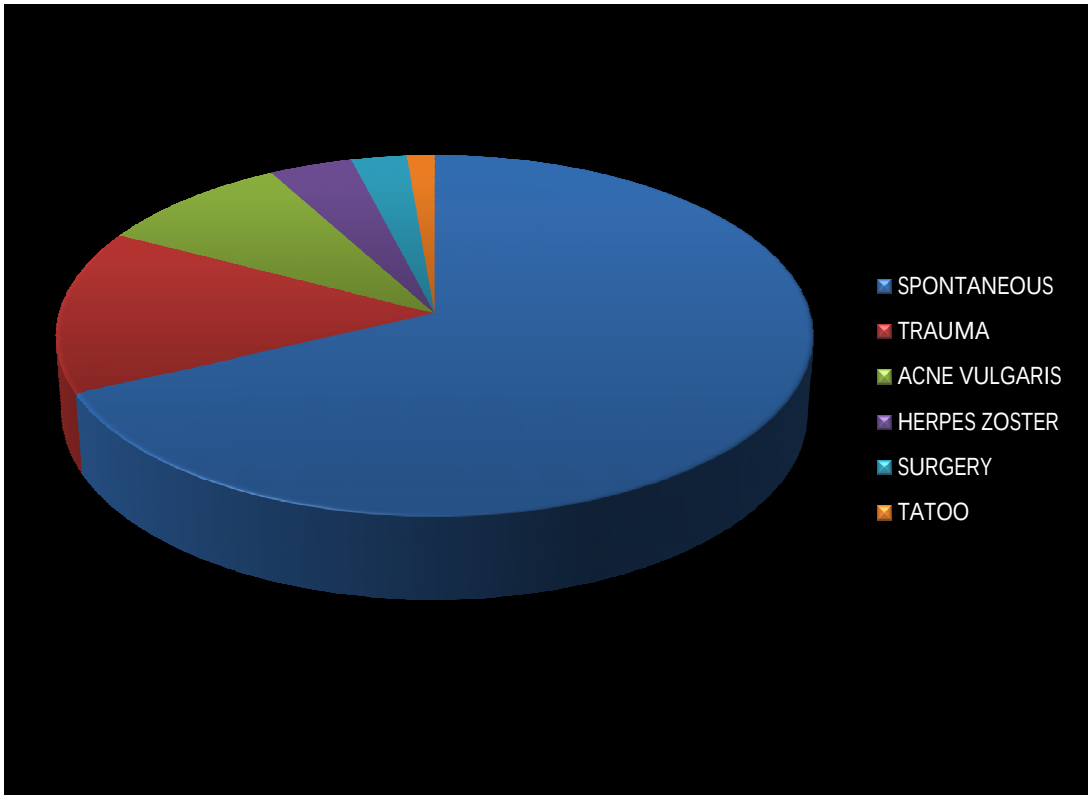
AGE AND SEX DISTRIBUTION



COMPARISON OF THE TREATMENT RESPONSES IN THE STUDY GROUPS:



ETIOLOGY OF KELOID



GROUP 1: PATIENTS TREATED WITH INTRALESIONAL TRIAMCINOLONE ACETONIDE (40MG/ML):

BEFORE TREATMENT

AFTER 18 WEEKS OF TREATMENT

GROUP 1: PATIENTS TREATED WITH INTRALESIONAL TRIAMCINOLONE ACETONIDE (40MG/ML):

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

GROUP 2: PATIENTS TREATED WITH INTRALESIONAL 5-FLOUROURACIL (50MG/ML):

BEFORE TREATMENT

AFTER 18 WEEKS OF TREATMENT

GROUP 2: PATIENTS TREATED WITH INTRALESIONAL 5-FLOUROURACIL (50MG/ML):

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

GROUP 3: PATIENTS TREATED WITH INTRALESIONAL VERAPAMIL (2.5MG/ML):

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

GROUP 3: PATIENTS TREATED WITH INTRALESIONAL VERAPAMIL (2.5MG/ML):

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

GROUP 4: PATIENTS TREATED WITH INTRALESIONAL 5-FLOUROURACIL (50 MG/ML) AND TRIAMCINOLONE (40MG/ML):

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

GROUP 4: PATIENTS TREATED WITH INTRALESIONAL 5-FLOUROURACIL (50 MG/ML) AND TRIAMCINOLONE (40MG/ML):

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

GROUP 5: PATIENTS TREATED WITH CRYOTHERAPY, TRIAMCINOLONE ACETONIDE (40 MG/ML) AND SILICONE GEL SHEETS:

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

GROUP 5: PATIENTS TREATED WITH CRYOTHERAPY, TRIAMCINOLONE ACETONIDE (40 MG/ML) AND SILICONE GEL SHEETS:

BEFORE TREATMENT:

AFTER 18 WEEKS OF TREATMENT:

SIDE EFFECTS OBSERVED DURING TREATMENT:

BLISTERING IN A PATIENT TREATED WITH 5- FLOUROURACIL:

SUPERFICIAL ULCERATION IN A PATIENT TREATED WITH

5- FLOUROURACIL:

PERILESIONAL HYPOPIGMENTATION IN A PATIENT TREATED WITH INTRALESIONAL TRIAMCINOLONE ACETONIDE:

TELANGIECTASIA IN A PATIENT TREATED WITH INTRALESIONAL TRIAMCINOLONE ACETONIDE:

KELOID AT THE SITE OF A TATOO

KELOIDS AT THE SITE OF HERPES ZOSTER:

PROFORMA

Name: **Age:** **Sex:** **IP No:** **Occupation:**

Address:

Phone No:

Complaints:

H/O Present Illness:

- Onset and duration of the lesion:
- H/O Pain:
- H/O Itching:
- H/O Burning Sensation:
- H/O Ulceration:
- H/O Discharge:
- H/O Trauma:
- H/O Sudden Increase In Size:
- H/O Vaccination:
- H/O Burns Or Scalds:
- H/O Varicella Infection:
- H/O Acne:
- H/O any other infected skin lesion:
- H/O Surgery:
- H/O Drug Intake:

Past H/O

- H/O Diabetes Mellitus, Hypertension, Thyroid Disease.
- H/O similar skin lesions elsewhere in the body in the past:

Family H/O

- H/O any other family members affected:

Personal H/O

- Diet:
- Alcoholism, Smoking:

Treatment H/O

H/O any treatment taken in the past:

General Examination

Built: Height: Weight: Pallor: Icterus:

Cyanosis: Lymphadenopathy: Clubbing:

Specific Features If Any:

Systemic Examination

CVS: RS: Abdomen:

CNS: Joints:

Dermatological Examination

Inspection

Number: Site: Length: Width: Height: Discharge:

Palpation

Warmth: Tenderness: Consistency:

Other Skin Lesions (If Any):

Nails: Oral and Genital Mucosa: Palms and soles:

Investigations

Complete Hemogram:

LFT:

RFT:

Fasting Lipid Profile:

Blood Group: X ray Chest: ECG and cardiac status:

Treatment Modality Chosen (Specify the Modality Chosen)

Side Effects and Response

	No of Weeks					
	3	**6**	**9**	**12**	**15**	**18**
Atrophy:						
Hyperpigmentation:						
Hypopigmentation:						

Telangiectasia:

Necrosis:

Ulceration:

Blistering:

Depigmentation:

Pain:

Assessment of Treatment Response:

	No of weeks						
	0	**3**	**6**	**9**	**12**	**15**	**18**

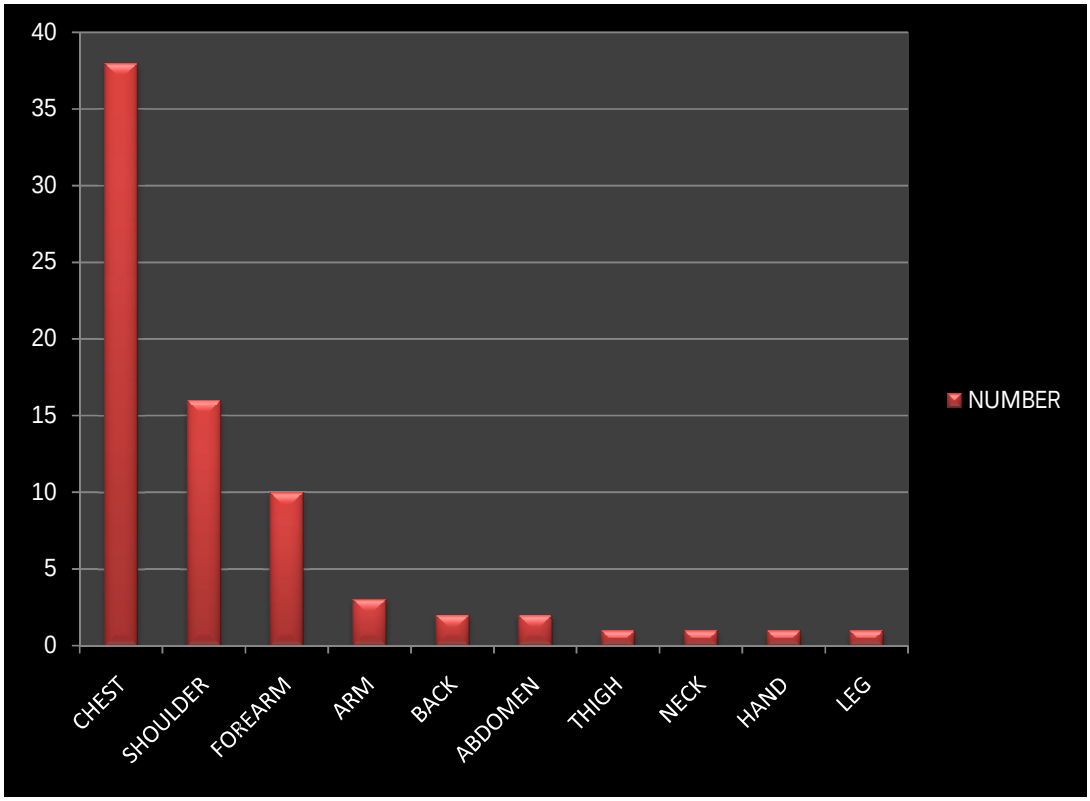
- **Height:**
  0 – Normal
  1 – < 2mm
  2 – 2 to 5mm
  3 – >5mm

- **Pigmentation:**
  0 – Normal
  1 – Hypopigmentation
  2 – Mixed
  3 – Hyperpigmentation

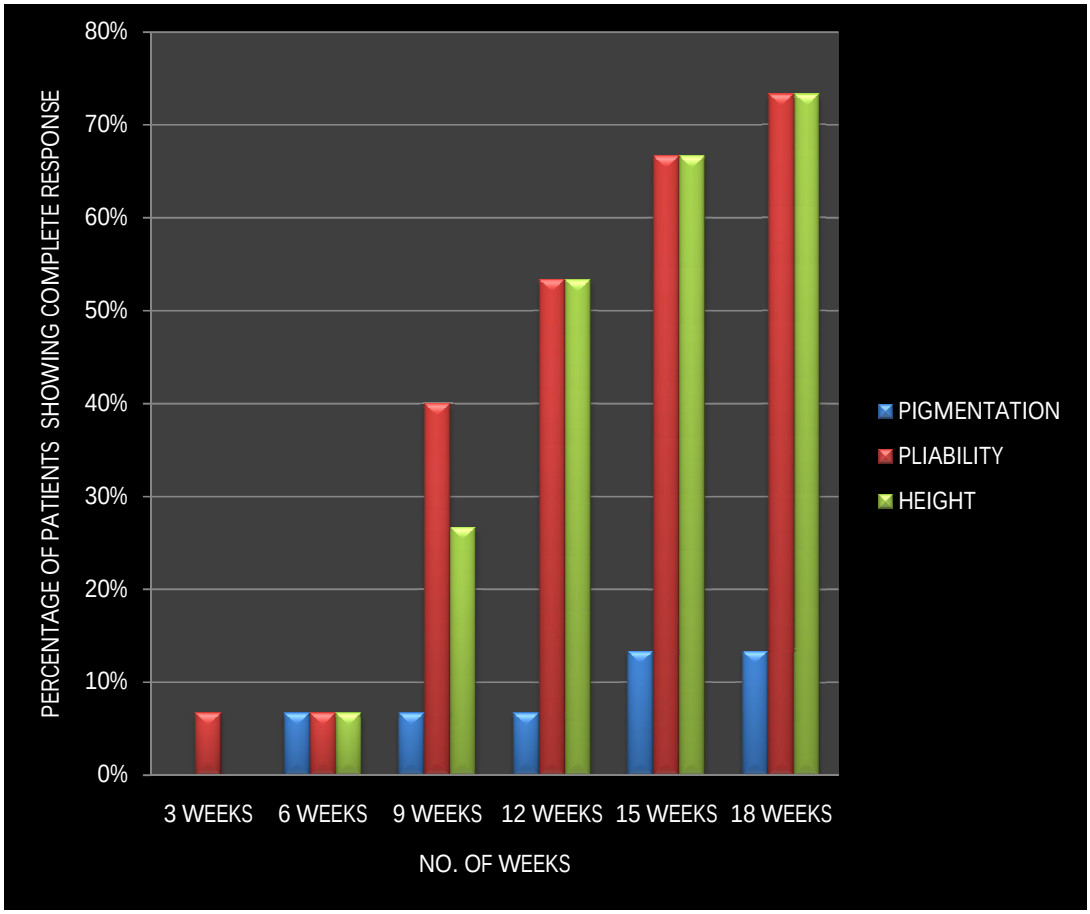
- **Pliability:**
  0 – Normal
  1 – Supple
  2 – Yielding
  3 – Firm
  4 – Banding
  5 – Contracture

- **Itching:**
  0 – No Itching
  1 – Sometimes Itchy
  2 – Moderate,tolerable itching
  3 – Severe, intolerable itching

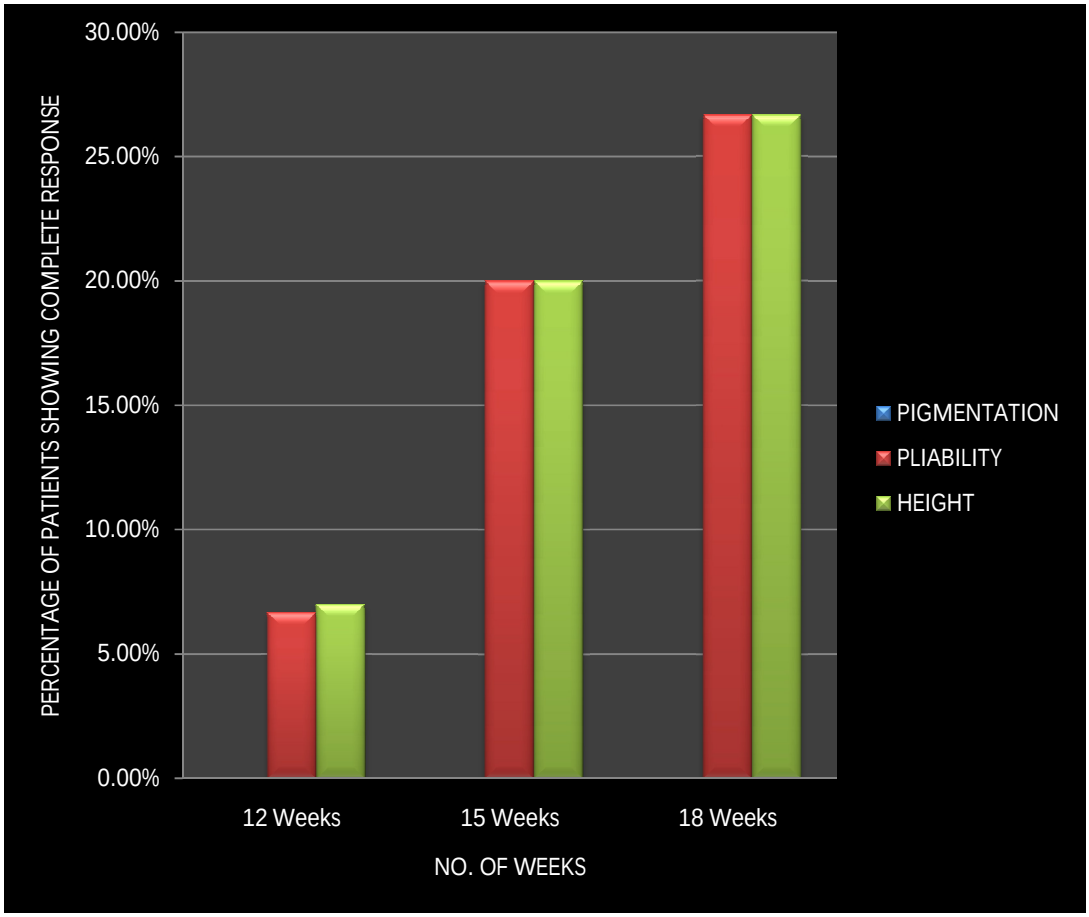
SITES OF INVOLVEMENT



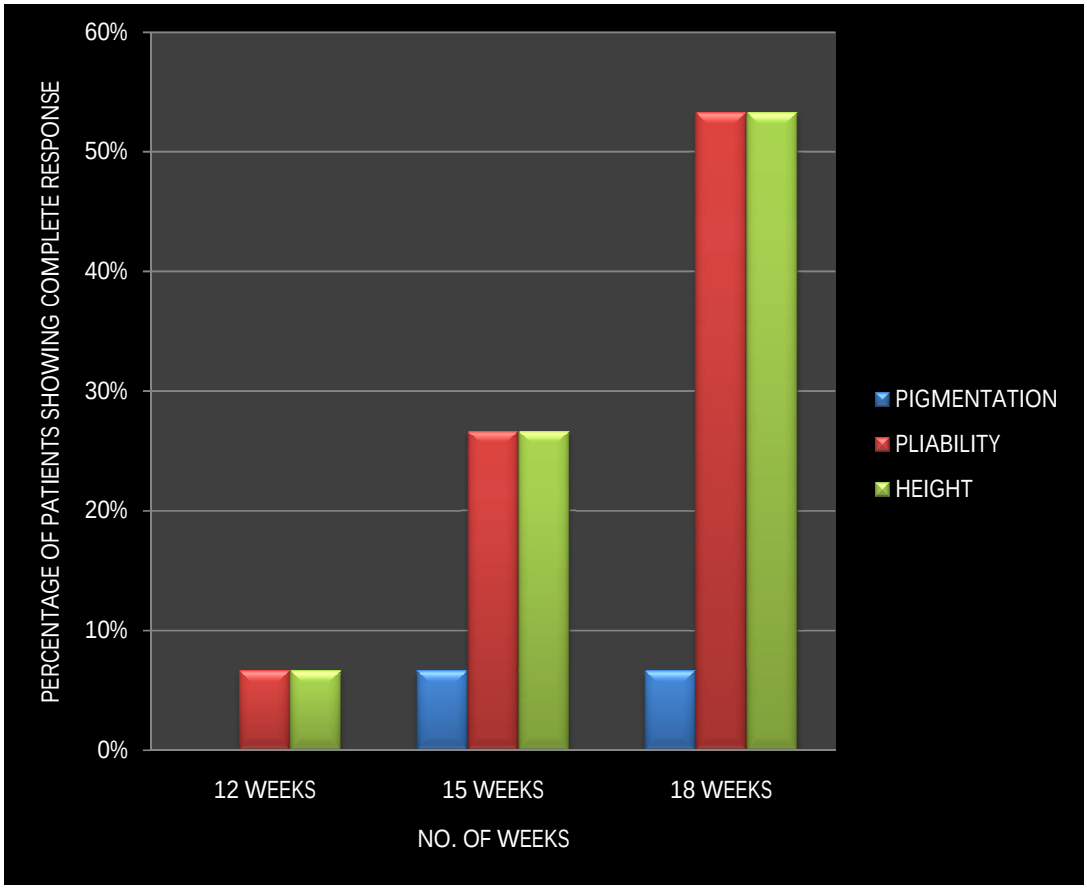
TREATMENT RESPONSE IN GROUP 1:



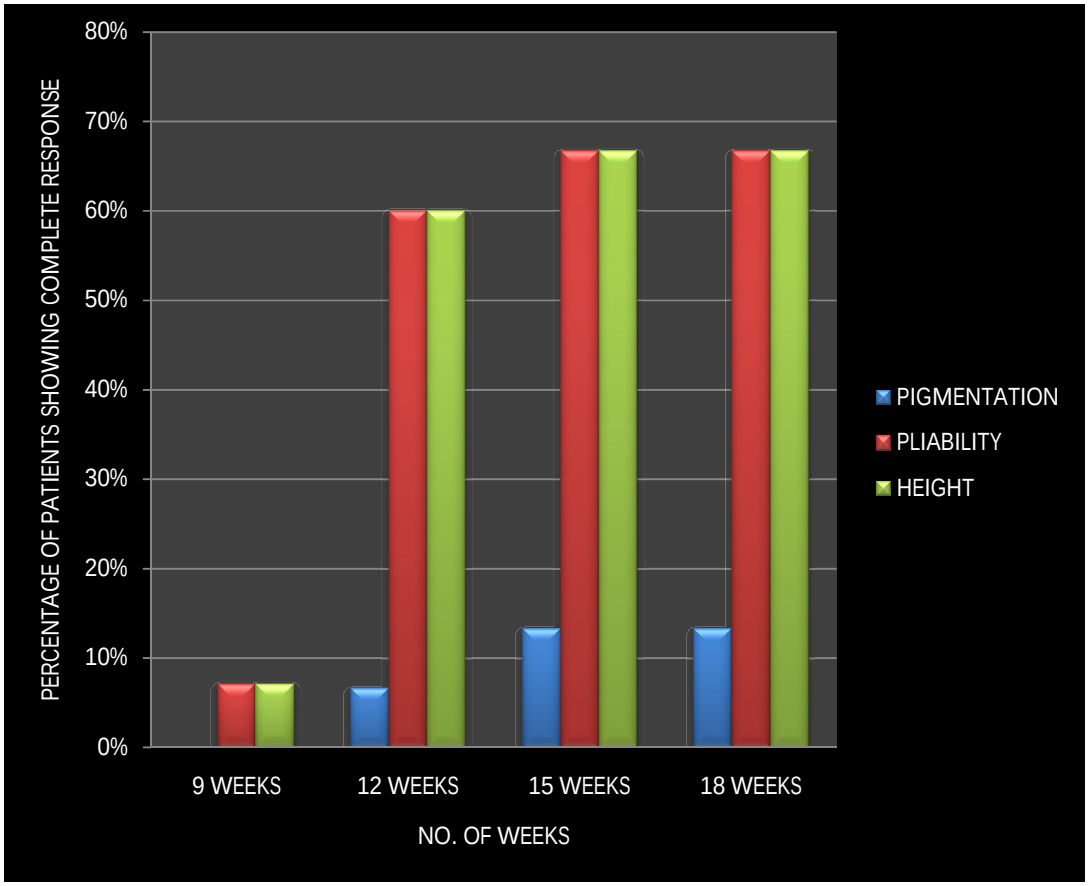
TREATMENT RESPONSE IN GROUP 2:



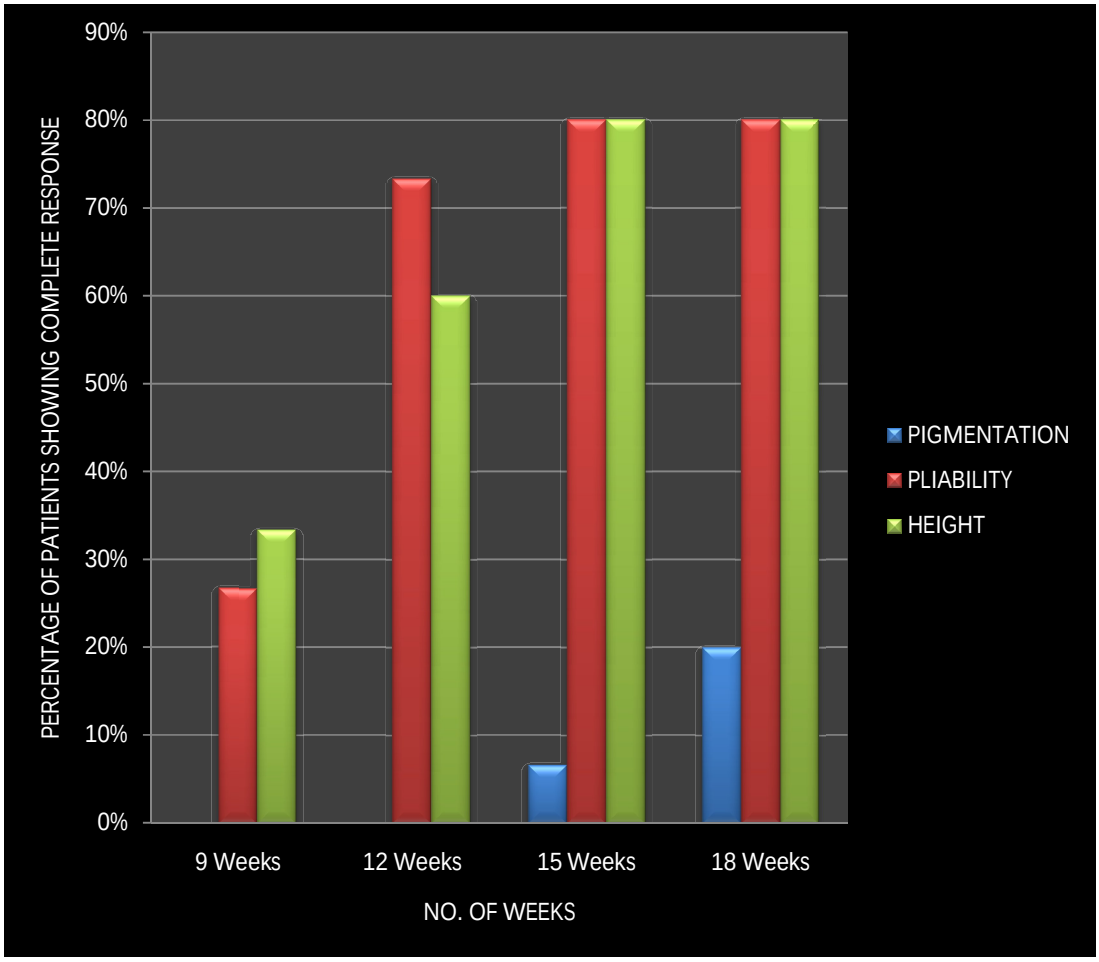
TREATMENT RESPONSE IN GROUP 3:



TREATMENT RESPONSE IN GROUP 4:



TREATMENT RESPONSE IN GROUP 5:



KEY TO MASTER CHART:

1. P - Pigmentation
2. PL – Pliability
3. H – Height
4. I – Itch
5. SPT – Spontaneous
6. HZ – Herpes zoster
7. M – Male
8. F - Female

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